REVIEW ARTICLE

The Risks Associated With Obesity in Pregnancy

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Summary

Background: Approximately one-third of all women of childbearing age are overweight or obese. For these women, pregnancy is associated with increased risks for both mother and child.

Methods: This review is based on pertinent publications retrieved by a selective search of PubMed, with special attention to current population-based cohort studies, systematic reviews, meta-analyses, and controlled trials.

Results: Obesity in pregnancy is associated with unfavorable clinical outcomes for both mother and child. Many of the risks have been found to depend linearly on the body-mass index (BMI). The probability of conception declines linearly, starting from a BMI of 29 kg/m^2, by 4% for each additional 1 kg/m^2 of BMI (hazard ratio 0.96, 95% confidence interval: [0.91; 0.99]). A 10% increase of pregravid BMI increases the relative risk of gestational diabetes and that of preeclampsia by approximately 10% each. A 5 kg/m^2 increase of BMI elevates the relative risk of intrauterine death to 1.24 [1.18; 1.30]. An estimated 11% of all neonatal deaths can be attributed to the consequences of maternal overweight and obesity. Nonetheless, in most randomized controlled trials, nutritional and lifestyle interventions did not bring about any clinically relevant reduction in the incidence of gestational diabetes and fetal macrosomia.

Conclusion: The risks associated with obesity in pregnancy cannot necessarily be influenced by intervention. Preventive measures aimed at normalizing body weight before a woman becomes pregnant are, therefore, all the more important.

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The prevalence of obesity (body mass index [BMI] ≥ 30 kg/m^2) among young women has increased in Germany over the last two decades. According to a survey conducted in 2013, 9.6% (n = 7116; 95% confidence interval (CI): [7.2; 12.7]) of all women between 18 and 29 years were obese (1). In the age group from 30 to 39 years, the prevalence increases to 17.9% [14.0; 22.7] (1). Class III obesity (BMI ≥ 40 kg/m^2) affects 0.9% [0.3; 2.7] of the 18- to 29-year-old and 2.3% [1.1; 4.6%] of the 30- to 39-year-old women (1). Combined, about one third of all women of reproductive age are overweight (BMI ≥ 25 to <30 kg/m^2, prevalence between 30 and 38%) or obese (1). Maternal and fetal morbidity risks associated with pregnancy will be discussed in the following.

Methods

A selective search primarily of the English literature was conducted in the PubMed database, using the following search terms: "obesity", "pregnancy", "female fertility", "miscarriage", "still birth", "mortality", "morbidity", "weight gain". Altogether 4002 hits were obtained for the past ten years up to and including December 2017.

Population-based cohort studies, randomized controlled trials, systematic reviews, and meta-analyses were preferentially included in the analysis. Relevant older papers identified in references or by targeted keyword search were also included.

Obesity and the desire to have children

Obesity-related hyperinsulinemia und subsequent hyperandrogenemia increase the risk for anovulatory cycles (2). The time until pregnancy occurs is longer in obese women compared to women of normal weight (3, e1–e3). The chance of conception within one year is already reduced starting at a BMI of 26 kg/m^2 (89.4% with a BMI of 20–25kg/m^2 versus 82.7% with a BMI >25 kg/m^2; n = 10 903) (4). Women with comorbidity were excluded from the analysis. The effect remained significant even after adjustment for possible confounding factors, such as age, parity as well as regularity and duration of the menstrual cycle (odds ratio [OR]: 0.77 [0.70; 0.84]). Thus, reduced fertility associ-

TABLE 1

Risks of maternal diseases in pregnancy in relation to body mass index

Disease	BMI 18.5–24.9		BMI ≥ 40		Adjusted OR	95% CI	Reference
	Prevalence (%)	Prevalence (n/N)	Prevalence (%)	Prevalence (n/N)			
Gestational diabetes	0.937	2185/233 160	9.292*[1]	1363/14 669*[1]	11.01	10.25–11.82	(9)
Gestational hypertensive disease	5.042	3351/66 463	17.262	536/3105	3.55*[2]	3.26–3.86	(7)
Preeclampsia	3.095	7217/233 160	10.641*[1]	1561/14 669*[1]	4.44	4.17–4.72	(9)
Eclampsia	0.037	131/353 212	0.070	22/31 392	2.3	1.4–3.7	(12)
Thromboembolic events	0.044	156/353 212	0.099	31/31 392	2.2	1.5–3.2	(12)
Cardiac morbidity	0.038	134/353 212	0.140	44/31 392	3.5	2.5–5.0	(12)
Respiratory morbidity	0.093	327/353 212	0.258	81/31 392	2.8	2.2–3.6	(12)
Cerebrovascular morbidity	0.064	225/353 212	0.134	42/31 392	2	1.4–2.8	(12)
Complications of anesthesia and obstetric interventions	0.149	528/353 212	0.245	77/31 392	1.5	1.2–2.0	(12)
Severe postpartum hemorrhage with transfusion	0.422	1489/353 212	0.312	98/31 392	0.7	0.6–0.9	(12)
Sepsis	0.323	1140/353 212	0.401	126/31 392	1.4	1.2–1.7	(12)
Obstetric shock	0.016	56/353 212	0.022	7/31 392	1.5	0.7–3.3	(12)
ICU admission	0.073	259/353 212	0.188	59/31 392	2.4	1.8–3.3	(12)
Combined severe maternal morbidity or mortality	1.432	5057/353 212	2.029	637/31 392	1.4	1.3–1.5	(12)

BMI, body mass index; ICU, intensive care unit; CI, confidence interval; n, cases per subgroup; N, size of the subgroup; OR, odds ratio
*[1] Data refer to BMI ≥ 35 kg/m^2
*[2] Adjusted risk ratio

ated with increasing BMI cannot only be attributed to menstrual irregularities (4, 5).

A study on women with regular ovulations desiring to have children (after exclusion of tubal and androgenic abnormalities, n = 3029) found that within one year 17% of subjects had a spontaneous pregnancy not ending in miscarriage (5). The likelihood of conception decreased in a linear fashion by 4% per 1 kg/m^2 weight gain, starting from a BMI of 29 kg/m^2; this finding remained significant even after adjusting for potential confounders (age, duration of desiring a child, pregnancy, smoking, sperm motility) (hazard ratio [HR]: 0.96 [0.91; 0.99]) (5).

Likewise, obesity had a negative impact on pregnancy rate and implantation rate after embryo transfer in autologous in vitro fertilization (IVF) (6, e4). A registry study from the US analyzing 239 127 IVF cycles showed that pregnancy rates and implantation rates declined by 1% with every increase in BMI by 5 kg/m^2 (6).

Maternal risks over the course of pregnancy

The risk of pregnancy-associated disorders increases with increasing severity of obesity (*Table* 1) (7–12). A 10% difference in pre-pregnancy BMI is associated with an at least 10% change in relative risk of preeclampsia and gestational diabetes, respectively (10). The obesity-associated increase in risk of not primarily pregnancy-related diseases is usually less pronounced (7–9, 12). Over the long term (≥ 10 years), a pre-pregnancy BMI >25 kg/m^2 is associated with an increased risk of manifestation of diabetes mellitus and cardiac disease. Gestational weight gain of more than 15 kg increases the risk of becoming obese later in life (13).

Fetal and neonatal risks

A pooled analysis of six studies comparing obese (n = 3800) with normal-weight women (n = 17 146) found an increased miscarriage rate after spontaneous conception (13.6% versus 10.7%, OR: 1.31 [1.18; 1.46]) (14). Likewise, recurrent miscarriage was more common in obese women (0.4% versus 0.1%, OR: 3.51 [1.03; 12.01]). A chromosomal analysis showed that euploid miscarriages occurred more frequently in obese women compared to normal-weight women (58% [18/31] versus 37% [32/86], risk ratio [RR]: 1.63 [1.08; 2.47], p = 0.02) (15). Maternal age and endocrine, autoimmune and inflammatory diseases were excluded as causative factors (15).

The prevalence of fetal malformations was significantly correlated with the severity of obesity (*Table 2*) and the risk increase was independent of gestational diabetes (16). Apart from that, a meta-analysis comprising 18 studies reported the following obesity-associated increases in risk for specific malformations:

- Spina bifida (n = 863, OR: 2.24 [1.86; 2.69], p <0.001)

TABLE 2

Congenital fetal malformation risks associated with maternal obesity

Malformation	BMI 18.5–24.9 (N = 756 432)		BMI ≥ 40 (N = 11 354)		Adjusted risk ratio	95% CI
	Prevalence (%)	Prevalence (n)	Prevalence (%)	Prevalence (n)		
Severe congenital malformations	3.40	25 713	4.70	529	1.37	1.26–1.49
Malformations of the nervous system	0.09	695	0.18	20	1.88	1.20–2.94
Congenital heart defect	1.56	11 807	2.26	257	1.44	1.27–1.63
Orofacial cleft	0.14	1070	0.21	24	1.44	0.96–2.16
Ocular malformations	0.19	1466	0.20	23	1.03	0.68–1.57
Gastrointestinal malformations	0.15	1134	0.23	26	1.54	1.05–2.28
Urinary tract malformations	0.34	2544	0.40	45	1.19	0.88–1.60
Genital malformations	0.46	3497	0.63	72	1.43	1.13–1.80
Limb malformations	0.35	2616	0.45	51	1.29	0.98–1.70
Other	0.21	1618	0.30	34	1.39	0.99–1.95

According to Persson et al. (16)
BMI, body mass index; CI, confidence interval; n, cases per subgroup; N, size of the subgroup

- Cardiac septal defects (n = 3483, OR: 1.20 [1.09; 1.31], p <0.001)
- Anorectal atresia (n = 273, OR: 1.48 [1.12; 1.97], p = 0.006
- Hydrocephalus (n = 188, OR: 1.68 [1.19; 2.36], p = 0.003) (17).

Only the risk of gastroschisis was lower with obesity (n = 379, OR: 0.17 [0.10; 0.30)], p <0.001). Furthermore, a cohort study evaluating 41 013 singleton pregnancies found that obesity increased the risk of eye anomalies (n = 1 versus n = 12; adjusted OR 6.30 [1.58; 25.08)], p = 0.009) (e5).

However, it has to be taken into account that ultrasound sensitivity was reduced due to unfavorable physical scanning conditions (e6). The decrease in fetal chromosomal fraction associated with obesity results in reduced detection rates for chromosomal aberrations, regardless of gestational age, in non-invasive prenatal testing (NIPT) too (e7).

The risk of intrauterine fetal death (IUFD) is increased in obese compared to normal-weight women (*Table 3*) (9). A meta-analysis calculated an adjusted risk ratio of 1.24 for a BMI increase by 5 kg/m^2 [1.18; 1.30] (18). While IUFD in women with a BMI of 20 kg/m^2 was observed in 0.4% of cases, the prevalence of IUFD in women with a BMI of 30 kg/m^2 was 0.59% [0.55; 0.63]. In the majority of cases, IUFD was caused by a combination of abnormal placental function and arterial hypertension (e8).

Similarly, maternal obesity is associated with an elevated postnatal mortality risk (first year of life) which increases with increasing BMI *(Table 3)* (19). The effect was more pronounced in term versus preterm neonates and had an effect on both early (≤ 28 days after delivery) and late mortality (>28 days after delivery). Even after women with concomitant hypertension and diabetes had been excluded, the association was still present: When comparing normal-weight versus BMI ≥40 kg/m^2 women, the adjusted OR was 2.24 [95% CI: 1.65; 3.03]. The authors calculated that 11% of deaths were associated with complications caused by overweight and obesity. Thus, with an annual infant mortality of about 2400 cases in Germany, 264 deaths could have been avoided. A sibling study confirmed the significance of maternal obesity as a risk factor for IUFD and postnatal mortality, regardless of genetic predisposition or familial factors (e9). Likewise, in initially normal-weight women a weight gain ≥2 kg/m^2 was associated with an increased risk of IUFD and postnatal mortality (20). Weight loss from an initial BMI of ≥ 25 kg/m^2 reduced the risk of neonatal mortality during the first 28 days after birth (20). Other studies confirmed the association between obesity and risk of IUFD and postnatal mortality (7, e10–e12).

Apart from an increased risk of asphyxia—which is also reflected in the increased infant cerebral palsy rates—causative factors included congenital anomalies and sudden infant death syndrome (19, e13, e14).

The preterm birth rate—both spontaneous and medically indicated due to pregnancy-associated conditions—is increased in obesity and contributes to the unfavorable neonatal outcome (21, 22, e15). The risk of medically indicated early preterm birth is primarily increased due to hypertensive and diabetic pregnancy complications (22). This risk is further increased in patients with gestational weight gain which is above the Institute of Medicine's recommendations of 5 to 9 kg from a BMI ≥30 kg/m^2 (meta-analysis with n = 3892, adjusted OR: 1.54 [1.09; 2.16]) (23, 24).

TABLE 3

Miscarriage risk: fetal and neonatal outcomes in relation to maternal body mass index

Parameter	BMI 18.5–24.9		BMI ≥ 40		Adjusted OR	95% CI	Reference
	Prevalence (%)	Prevalence (n/N)	Prevalence (%)	Prevalence (n/N)			
Miscarriage (≤ 20 weeks' gestation)	7.8	257/3302	14.3	51/359	2.49	1.45–4.26	(e52)
Intrauterine fetal death (>22 weeks' gestation)	0.253	589/233 160	0.559*1	82/14 669*1	1.86	1.39–2.47	(9)
Postnatal mortality (1st year of life)	0.236	2393/1 014 513	0.580	63/10 855	2.44	1.88–3.17	(19)
5-min APGAR <7	0.538	1254/233 160	1.043*1	153/14 669*1	1.94	1.63–2.32	(9)
Birth weight >4500 g	2.4	5697/233 160	6.4*1	940/14 669*1	2.74	2.55–2.95	(9)
Preterm birth (22–27 weeks' gestation)	0.17	1703/1 014 513	0.52	56/10 855	2.91	2.21–3.81	(22)
Asphyxia (10-min APGAR: 0–3) in neonates ≥ 37 + 0 weeks' gestation	0.045	431/961 710	0.120	12/9987	3.41	1.91–6.09	(e13)
Meconium aspiration syndrome	0.45	297/66 463	0.90	28/3105	1.81*2	1.22–2.67	(7)
Neonatal sepsis	2.06	1367/66 463	3.83	119/3105	1.55*2	1.28–1.87	(7)
Neonatal ICU	8.85	5880/66 463	14.46	449/3105	1.38*2	1.26–1.51	(7)
Cerebral palsy	0.189	1487/787 815	0.365	38/10 413	2.02*3	1.46–2.79	(e14)

BMI, body mass index; ICU, intensive care unit; CI, confidence interval; n, cases per subgroup; N, size of the subgroup; OR, odds ratio;
5-min/10-min APGAR, scores of neonate assessment 5/10 minutes after delivery
*1 Data refer to BMI ≥ 35 kg/m^2
*2 Adjusted risk ratio
*3 Adjusted hazard ratio

The situation is similar for weight gain between two pregnancies. In women with first pregnancy BMI <25, the risk of spontaneous preterm birth (32 to 36 weeks' gestation) increases by adjusted 18% when the BMI increases by ≥4 kg/m^2 compared to baseline level [5; 33%], p = 0.007, n = 305 953) (e16).

Fetal macrosomia and postnatal metabolic consequences

Maternal obesity increases the risk of fetal macrosomia, as demonstrated by the results of a meta-analysis including 21 studies: 13.4% with obesity (n = 31 756) versus 7.8% with normal weight (n = 57 392, pooled OR: 2.11 [1.97; 2.27]) (25). Here again, maternal gestational weight gain was an additional independent risk factor (e17, e18). Neonates of obese mothers had a higher percentage of adipose tissue (e19, e20). A study evaluating 112 309 deliveries of women without chronic disease prior to pregnancy showed that the percentage of fetal macrosomia ("large for gestational age", LGA) rose with increasing maternal BMI, amounting to 17% (538/3105) among ≥40 kg/m^2 women (2.76% of the cohort) compared to 8% (5272/66 463) among normal-weight mothers (RR: 2.32 [2.14; 2.52], p <0.001) (7). This association remained even after exclusion of all cases with gestational hypertensive disease and gestational diabetes (14.7% [n = 327] in pregnant women with class III obesity versus 7.9% [n = 4863] with normal weight, RR: 2.04 [1.83; 2.26], p <0.001). Further studies confirmed that obesity is a risk factor for fetal macrosomia, independent of a diabetic metabolic state (26, e21). The pathogenesis of fetal macrosomia is complex. On the one hand, macrosomia appears to be the consequence of increased maternal blood glucose levels, resulting from obesity-related insulin resistance which can already be detected below the diagnostic threshold for gestational diabetes (26, 27, e22). This is supported by the close correlation between maternal fasting glucose levels and fetal weight (23, 28, e17). On the other hand, however, the increase in percentage of adipose tissue in the neonate can only be explained to a limited extent by the increased availability of metabolic substrates (28). After including placental mass as a covariate in multiple regression analysis, BMI-related metabolic changes correlating with neonatal body fat mass were no longer significant (e23). This highlights the important role of the placenta as a nutritive sensor, actively influencing the metabolic regulation of maternofetal interactions (e24, e25).

Fetal macrosomia, maternal obesity and excessive weight gain during pregnancy are associated with later obesity in childhood and adolescence (e26, e27). As early as at age 6 years, children of women who were obese before they became pregnant had more often a cardiometabolic risk profile compared to children of normal-weight mothers: 22.4% (54/404) versus 8.3% (144/2789), p <0.01; OR: 3.0 [2.09; 4.34]) (e28). After adjusting for the children's BMIs, these differences were no longer significant; thus, the changes (parameters assessed: android fat distribution pattern, blood pressure, blood lipid levels, serum insulin and C-peptide levels) are significantly influenced by the increased risk of weight gain these

TABLE 4

Obstetric outcome parameters: risk in relation to pre-pregnancy body mass index

Condition	BMI 18.5–24.9		BMI ≥ 40		Adjusted OR/RR	95% CI	Reference
	Prevalence (%)	Prevalence (n/N)	Prevalence (%)	Prevalence (n/N)			
Induction of labor	38.9	23 775/61 140	48.6	1218/2505	1.39*2	1.34–1.45	(7)
Cesarean sections (total)	22.4	14 872/66 463	46.9	1457/3105	2.01*2	1.93–2.10	(7)
Primary C-section (prior to start of labor)	8.0	5323/66 463	19.3	600/3105	2.02*2	1.88–2.18	(7)
Emergency cesarean section	9.9	22 974/233 160	17.2	2529/14 669*1	2.11	2.01–2.21	(9)
Premature placental abruption	1.4	937/66 463	1.6	51/3105	0.84*2	0.63–1.11	(7)
Perineal tear, III/IV degree	3.4	1571/n.a.	1.6	24/n.a.	0.68*2	0.46–1.02	(7)
Puerperal fever	1.7	1132/66 463	2.7	83/3105	1.37*2	1.10–1.71	(7)
Severe puerperal infection	0.4	260/66 463	0.7	23/3105	1.75*2	1.15–2.68	(7)
Postoperative wound healing complications	0.3	209/66 463	0.6	19/3105	2.17*2	1.34–3.51	(7)
Complications of anesthesia and obstetric interventions	0.149	528/353 212	0.245	77/31 392	1.5	1.2–2.0	(12)
Severe postpartum hemorrhage with transfusion	0.422	1489/353 212	0.312	98/31 392	0.7	0.6–0.9	(12)
Sepsis	0.323	1140/353 212	0.401	126/31 392	1.4	1.2–1.7	(12)
Obstetric shock	0.016	56/353 212	0.022	7/31 392	1.5	0.7–3.3	(12)
ICU admission	0.073	259/353 212	0.188	59/31 392	2.4	1.8–3.3	(12)
Combined severe maternal morbidity or mortality	1.4	5057/353 212	2.0	637/31 392	1.4	1.3–1.5	(12)

BMI, body mass index; ICU, intensive care unit; CI, confidence interval; n.a., data not available; OR, odds ratio; RR, risk ratio
*1 Data refer to BMI ≥ 35 kg/m^2
*2 adjusted risk ratio

children are exposed to. Similar results were found for maternal weight gain during early pregnancy (e29). These associations can still be demonstated at age 17 years (e29).

Intra- and post-partum risks

The risks culminate at the time of delivery and apply to mother and infant *(Table 4)*. The likelihood of vaginal delivery decreases with increasing obesity (8, 11, e30). Even though cesarean sections are more commonly performed in obese mothers (7–9), attempts of vaginal delivery are successful in 73% of primiparas and 94% of multiparas (e31). Conditions underlying the increased cesarean section rate include preeclampsia, fetal distress, cephalopelvic disproportion, and failure to progress in labor (11, e32). However, due to wound infection and wound healing abnormalities, surgery-associated morbidity is also increased in obese women (7, 8, 11). Epidural analgesia is often unsuccessful (e33). Early administration of epidural anesthesia can be advantageous as, in case an emergency cesarean section is indicated at a later stage of labor, it avoids the risks associated with general anesthesia (e34).

The risk of shoulder dystocia is not or only insignificantly increased by obesity alone (8, 9). The largest study on this risk found a significant association between BMI and shoulder dystocia (incidence in the total population: 0.9%, OR: 2.0 [1.73; 2.37] for BMI ≥35 kg/m^2) (9). However, after adjustment this association was no longer significant (adjusted OR: 1.2 [0.98; 1.37]). The covariates birth weight, gestational diabetes, and gestational age were individually not significant; thus, it appears that the risk increase observed without adjustment is the result of the interaction of these risk factors (9).

Intervention options for maternal obesity

The *eTable* provides an overview over current randomized controlled trials and *Table 5* over obesity-related meta-analyses aiming to improve pregnancy outcomes. Lifestyle interventions comprise dietary changes and physical activity. In women desiring to have children, these interventions can increase ovulation and spontaneous conception rates (29, 30, e35, e36). However, patients already scheduled for assisted reproduction treatment did not benefit from weight reduction (30).

At best, a weight reduction of 10 to 15% within one year can be expected from lifestyle interventions. Weight loss of 30 to 40% is often achieved in the first year after bariatric surgery (e37). The largest published case–control study evaluating the effect of bariatric surgery found significant reductions in the prevalences of gestational diabetes and fetal macrosomia, but also an increased risk of fetal hypotrophy (15.6% [92/590] versus 7.6% [178/2336], adjusted

TABLE 5

Meta-analyses on the reduction of obesity-associated pregnancy risks (selection)

Study	Intervention	Control	Endpoint	N	Outcome	Comment
Tieu et al. 2017 (34)	Dietary intervention	Standard antenatal care	GDM	5 RCTs, n = 1279	7.6% vs. 12.6%, RR: 0.60, 95% CI: [0.35; 1.04], p = 0.07	Risk reduction possible, very low quality, I^2 = 56%, Subgroup analysis with greater advantage in overweight and obesity
			Gestational weight gain	5 RCTs, n = 1336	Mean difference: –4.70 kg, 95% CI: [–8.07; –1.34]	Effect likely, low quality, I^2 = 96%
	Dietary intervention with low glycemic index (GI)	Diet with moderate to high GI	GDM	4 RCTs, n = 912	RR: 0.91, 95% CI: [0.63; 1.31]	No differences, low quality
			LGA	3 RCTs, n = 777	RR: 0.60, 95% CI: [0.19; 1.86], p = 0.07	No differences, very low quality, I^2 = 62%
Shepherd et al. 2017 (35)	Combination of diet and physical activity	Standard antenatal care	GDM	19 RCTs, n = 6633	14.3% vs. 16.8% RR: 0.85, 95% CI: [0.71; 1.01], p = 0.07	Risk reduction possible, moderate quality, I^2 = 42%, subgroup analysis taking into account BMI without clearly changed treatment effects
			Cesarean section	14 RCTs, n = 6089	28.4% vs. 29.9% RR: 0.95, 95% CI: [0.88; 1.02]	Risk reduction possible, moderate quality
			Preeclampsia	8 RCTs, n = 5366	5.5% vs. 5.7% RR: 0.98, 95% CI: [0.79; 1.22]	No risk reduction, low quality
			PIH	6 RCTs, n = 3073	8.0% vs. 10.3% RR: 0.78, 95% CI [0.47; 1.27]	No risk reduction, very low quality, I^2 = 62%
			Gestational weight gain	16 RCTs, n = 5052	Mean difference: –0.89 kg, 95% CI: [–1.39; –0.40]	Effect likely, moderate quality, I^2 = 43%
Muktabhant et al. 2015 (33)	Dietary or lifestyle intervention or both combined	Standard antenatal care	Increased gestational weight gain	24 RCTs, n = 7096	36.2% vs. 45.3% RR: 0.80, 95% CI: [0.73; 0.87]	Risk reduction demonstrated, high quality, I^2 = 52%, no differences with regard to shoulder dystocia, obstetric injury, neonatal hypoglycemia, hyperbilirubinemia
			Preeclampsia	15 RCTs, n = 5330	6.2% vs. 6.6% RR: 0.95; 95% CI: [0.88; 1.03]	No risk reduction, high quality, I^2 = 0%
			Cesarean section	28 RCTs, n = 7534	27.4% vs. 28.8% RR: 0.95, 95% CI: [0.88; 1.03]	No risk reduction, high quality, I^2 = 9%
			Birth weight >4000 g	27 RCTs, n = 8598	16.6% vs. 17.8% RR: 0.93, 95% CI: [0.86; 1.02]	No risk reduction, high quality, I^2 = 0%, subgroup analysis in overweight/obese women or with otherwise increased GDM risk showed risk reduction: RR: 0.85; 95% CI: [0.73; 1.00], p = 0.05
Magro-Malosso et al. 2017 (e49)	Aerobic exercise (30–60 min, 3–7 × weekly) with BMI ≥ 25 kg/m^2	Standard antenatal care	Preterm birth <37 weeks' gestation	9 RCTs, n = 1502	4.2% vs. 5.6% RR: 0.62, 95% CI: [0.41; 0.95]	Risk reduction demonstrated, I^2 = 27%, gestational age at time of delivery not different (mean difference of 0.09 weeks)
i-WIP Collaborative Group 2017 (37)	Diet (4 studies), physical activity (16 studies), combination of the two (16 studies)	Standard antenatal care	Gestational weight gain	33 RCTs, n = 9320	10.1 kg vs. 10.8 kg mean difference: −0.70, 95% CI: [–0.92; –0.48]	High significance because analysis of individual patient data (36 RCTs, n = 12 526, 40% obesity); effects small to moderate, I^2 = 14%, no sigtnficant change due to covariate BMI
			GDM	27 RCTs, n = 9427	13.5% vs. 14.5% OR: 0.89, 95% CI: [0.72; 1.10]	Risk reduction possible, I^2 = 23%, Significant effect in the subgroup with only physical activity
			Hypertensive disorders	22 RCTs, n = 9618	9.4% vs. 10.1% OR: 0.95; 95% CI: [0.78; 1.16]	No risk reduction, I^2 = 24%
			Cesarean section	32 RCTs, n = 11 410	34.8% vs. 37.7% OR: 0.91, 95% CI: [0.83; 0.99]	Risk reduction demonstrated, I^2 = 0%
			LGA (>90th percentile)	34 RCTs, n = 12 047	13.5% vs. 15.0% OR: 0.90, 95% CI: [0.76; 1.07]	No risk reduction, I^2 = 38%

BMI, body mass index; GDM, gestational diabetes; GI, glycemic index; I^2,measure of heterogeneity as defined by Higgins/Thompson; CI, confidence interval; LGA, large for gestational age; OR, odds ratio; ; RCT, randomized controlled trial; RR, risk ratio; PIH, pregnancy-induced hypertension

OR: 2.2 [1.64; 2.95], p <0.001) (e38). Furthermore, a trend towards increased perinatal mortality was observed (1.7% [10/596] versus 0.7% [17/2356], adjusted OR: 2.39 [0.98; 5.85], p = 0.06) (e38). In another analysis, status post bariatric surgery was associated with an increased risk of preterm birth >32 weeks' gestation (7.3% [139/1917] versus 5.7% [369/6496], adjusted OR: 1.30 [1.05; 1.60], p = 0.01) (e37, e39). Matching criteria for the control group included preoperative BMI, age, and parity. The groups were homogeneous with regard to comorbidities, such as diabetes mellitus and cardiovascular disease. The cause(s) underlying the observed risk increase remain unclear; impaired nutrition due to malassimilation and metabolic-endocrine adjustments due to the changed fat distribution pattern have been discussed as possible explanations (e37, e40, e41).

Weight loss during pregnancy is associated with a heightened risk of neonatal hypotrophy (e42, e43). Thus, despite the inconsistency of the available data (e44), weight reduction during pregnancy is not usually recommended (e34, e43). By contrast, weight loss between 2 pregnancies has a positive effect on neonatal outcomes (e45). After delivery, however, mothers are generally poorly motivated to actively reduce weight (e46).

Metformin treatment of obese pregnant women was evaluated in 2 randomized controlled trials where it reduced weight gain during pregnancy but did not lower the risk of gestational diabetes and neonatal macrosomia (31, 32).

Gestational weight gain was also reduced by lifestyle interventions; however, no or no clinically relevant reduction of maternal or fetal morbidity was observed in these studies (33–39, e47–e51). However, it appears that intensive and supervised physical activity started early in pregnancy (during first 3 months) can reduce maternal blood glucose levels and the rate of gestational diabetes to a clinically relevant degree (40).

Conclusion

Obesity-related maternal and fetal increases in morbidity during pregnancy are well supported by evidence from studies. Obesity is a risk factor independent of comorbidities such as diabetes. The same applies to excessive weight gain during pregnancy. There is growing evidence that the placenta plays an important role in the regulation of fetal growth. Treatment strategies appear to be promising, provided the following conditions are met:

- High-level adherence and monitoring of intervention by supervision of the training program
- Start of intervention prior to or concomitant with placental development to prevent irreversible negative metabolic conditioning.

In principal, weight normalization prior to getting pregnant is advantageous. Ultimately, long-term reduction of maternal and fetal morbidity can only be achieved by dietary and lifestyle changes maintained beyond pregnancy.

KEY MESSAGES

- Overweight and obesity during pregnancy result in increased maternal and fetal morbidity in relation to BMI.
- An increase in pre-pregnancy body mass index by 10% is associated with an about 10% increase in the risk of gestational diabetes/preeclampsia.
- The reduction of fertility associated with obesity cannot be fully attributed to abnormalities of the menstrual cycle.
- The majority of studies on dietary and life-style interventions during pregnancy failed to show any clinically relevant maternal and fetal benefits.
- Potential reasons for the lack of evidence in support of the effectiveness of these interventions include the frequently vaguely defined level of dietary and exercise interventions in obesity, poor analyzability of the intervention due to lack of patient adherence, and very late start of intervention.

Conflict of interest statement
The authors declare that no conflict of interests exists.

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► **Supplementary material**
For eReferences please refer to
www.aerzteblatt-international.de/ref1618

eTable:
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eTABLE

Randomized controlled trials on the reduction of obesity-associated pregnancy risks (selection)

Study	Intervention	Control	Endpoint	Outcome	Comment
van Oers et al. 2016 (e36), Mutsaerts et al. 2016 (30) (LIFEstyle study)	Infertile patients with BMI ≥ 29 kg/m^2: 6-month intervention aiming to achieve 5–10% weight loss (dietary counselling and daily moderate physical exercise of at least 2–3 × 30 min/week, followed by fertility treatment) (n = 280)	Immediate fertility treatment (n = 284)	Vaginal delivery of a term infant within a period of 2 years	27.1%vs. 35.2% Rate ratio: 0.77, 95% CI: [0.60; 0.99]	Lifestyle intervention inferior with regard to primary EP (average weight reduction of 4.4 ± 5.8 kg achieved by the intervention); the set weight reduction goal was reached in 38% of cases; early termination of the intervention by 22% of subjects; per-protocol analysis: no difference in pregnancy rates and no difference when including the women pregnant after 2 years
			Spontaneous conception within a period of 2 years	26.1% vs. 16.2% OR: 1.83, 95% CI: [1.21; 2.76]	The intervention increased the likelihood of spontaneous conception (anovulation rate of 46.9% [269/574], of these 75% [201/269] with PCOS)
Legro et al. 2015 (29)	Infertile PCOS patients with BMI of 27–42 kg/m^2: 16-week lifestyle intervention (diet, sibutramine/orlistat, physical exercise) ± oral contraception, followed by 4 cycles of clomiphene treatment (n = 100)	16 weeks only oral contraception, then 4 cycles of clomiphene treatment (n = 49)	Live births	25.0% vs. 10.2% (p = 0.05)	Marginally significant effectiveness with combined analysis of both lifestyle intervention arms (with/without OC); secondary combined analysis of the data with a further study showed significant advantage of intervention (RR: 2.5, 95% CI: [1.3; 4.8], p = 0.01) (e35)
Dodd et al. 2016 (LIMIT) (36)	BMI ≥ 25 kg/m^2 (10–20 weeks' gestation): dietary/nutritional advice, Promotion of physical activity, behavioral advice (n = 488)	Standard antenatal care (n = 482)	Percentage neonatal body fat mass	14.41% vs. 14.37% adjusted treatment effect: 0.03. 95% CI: [–0.43; 0.48], p = 0.91	No change in body fat composition and obesity rate
Poston et al. 2015 (UPBEAT) (38)	BMI ≥ 30 kg/m^2 (15–18 weeks' gestation): 8 × weekly behavioral advice, recommendations for physical activity and diet, self-monitoring (n = 761)	Standard antenatal care (n = 651)	GDM (primary maternal EP)	25% vs. 26% RR: 0.96, 95% CI: [0.79; 1.16], p = 0.68	Despite significant reduction in gestational weight gain, no impact on primary EP; no advantage regarding maternal and fetal morbidity (secondary EP); 6-month follow-up with significantly lower subscapular skin fold thickness in the intervention group (infant); persistent low
			Birth weight >90th percentile (primary fetal EP)	9% vs. 8% RR: 1.15, 95% CI: [0.83; 1.59], p = 0.40	
Wang et al. 2017 (40)	BMI ≥ 24 kg/m^2 (<13 weeks' gestation): at least 3 × weekly supervised activity (bicycle ergometer 30–45–60 min changing intensity) (n = 132)	Standard antenatal care (n = 133)	GDM	22.0% vs. 40.6% OR: 0.41, 95% CI: [0.24; 0.71], p <0.001	Study population: Obesity in 26%; mean BMI of 26.8 kg/m^2; GDM incidence cut by about half; significant reduction in BG levels in oGTT with 75 g; significant reduction in gestational weight gain; strict training program with high adherence: 90% of subjects completed at least 80% of training program; training start already in 1st trimester; no dietary program; no difference regarding hypertensive disorders, including preeclampsia; no significant difference in LGA, but trend (OR: 0.56, 95% CI: [0.28; 1.12])
Garnaes et al. 2016 (e53), Garnaes et al. 2017 (e54) (ETIP)	BMI ≥ 28 kg/m^2 (<18 weeks' gestation): 3 × weekly supervised activity (treadmill 35 min, strength training 25 min; in addition, 1 × weekly 50 min home exercising) (n = 38)	Standard antenatal care (n = 36)	Gestational weight gain	10.5 kg vs. 9.2 kg Mean difference: 1.29, 95% CI: [−1.58; 4.05], p = 0.35	No significant difference; no trend; small study population; only 50% adherence according to protocol; analysis of secondary EP without reduction of GDM prevalence (WHO definition 2013)

Simmons et al. 2017 (DALI) (39)	BMI ≥ 29 kg/m^2 (<20 weeks' gestation): 3 intervention arms: 1. dietary interventions (n = 76) 2. physical activity (n = 74) 3. combination (n = 75)	Standard antenatal care (n = 79)	Gestational weight gain	8.0 kg (diet) vs. 8.5 kg (activity) vs. 6.5 kg (combination) vs. 8.8 kg (control) Mean difference combination vs. control: –2.02, 95% CI: [−3.58; –0.46], p <0.05	Intervention with nutritional counseling (7 ×) and/or counselling on physical activity (5 ×); study inclusion at 15 weeks' gestation on average; combined intervention with reduction in weight gain; each intervention alone without significant effect; no reduction in metabolic parameters (HOMA-IR, glucose, GDM); no reduction in LGA rate
Sagedal et al. 2017 (Fit for Delivery) (e50, e51)	BMI ≥ 19 kg/m^2 (≤ 20 weeks' gestation): dietary advice (2 × over the phone) and 2 × weekly physical activity (40 min moderate exercising) (n = 296)	Standard antenatal care (n = 295)	Gestational weight gain	14.4 kg vs. 15.8 kg Mean difference: 1.3, 95% CI: [0.3; 2.3], p = 0.009	Effect demonstrated; 28% of subjects with overweight/obesity; no risk reduction for GDM; intervention without effect on BG levels, but with significant reduction in insulin and leptin levels; subgroup analysis: with obesity risk of abnormal oGTT increased
Koivusalo et al. 2016 (RADIEL) (e48)	BMI ≥ 30 kg/m^2 (<20 weeks' gestation) and/or history of GDM: dietary advice and individual physical activity program (target at least 120 min moderate exercising/week) (n = 155)	Standard antenatal care (n = 138)	GDM	13.9% vs. 21.6% Adjusted RR: 0.61, 95% CI: [0.40; 0.98], p = 0.044	Inclusion at 13 weeks' gestation on average; no differences for PIH, preeclampsia, cesarean section, birth weight, macrosomia >4500 g; 39% risk reduction for GDM with moderate lifestyle intervention in a high-risk group
Chiswick et al. 2015 (EMPOWaR) (31)	BMI ≥ 30kg/m^2 (12–16 weeks' gestation): metformin 500–2500 mg/day orally from study inclusion through to delivery (n = 226)	Placebo (n = 223)	Neonatal weight percentile, birth weight	3462 g vs. 3462 g Mean difference of effect size: –0.029, 95% CI: [−0.217; 0.158], p = 0.76	Significantly more side effects: diarrhea 42% vs. 19% (p <0.0001), vomiting 32% vs. 22% (p = 0.03); no effect on primary and secondary EPs
Syngelaki et al. 2016 (MOP) (32)	BMI >35 kg/m^2 (12–18 weeks' gestation): metformin 500–3000 mg/day orally from study inclusion through to delivery (n = 202)	Placebo (n = 198)	Neonatal weight percentile	Z score: 0.05 vs. 0.17, p = 0.66	No effect on neonatal weight percentile, but significantly lower maternal weight gain during pregnancy

BMI, body mass index; BG, blood glucose; EP, end point; GDM, gestational diabetes; HOMA-IR, homeostasis model assessment—insulin resistance; CI, confidence interval; LGA, large for gestational age; OC, oral contraception; oGTT, oral glucose tolerance test; PCOS, polycystic ovary syndrome; PIH, pregnancy-induced hypertension; WHO, World Health Organization